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The evaluation and management of shock

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Shock is recognized at the bedside when hemodynamic instability leads to hypoperfusion of several organ systems. Accordingly, shock is a clinical diagnosis. Successful management of shock requires a primary survey directed at formulation of a working diagnosis and urgent initial resuscitation. The clinical response to initial measures to restore organ perfusion then confirms or changes the working diagnosis. This allows the clinician a pause to ponder the broader differential diagnosis of the types of shock and the pathophysiology of shock, which leads to early definitive therapy of the underlying cause of shock. Shock has a hemodynamic component, which is the initial focus of resuscitation, but shock also has a systemic inflammatory component that leads to multiple system organ failure. In this article, we present a simplified approach to diagnosis and management of shock and emphasize the tempo of resuscitation. The ultimate goal is to restore tissue perfusion in a timely fashion to prevent the development of multiple organ failure, which has a high mortality.

Shock is a clinical diagnosis

Shock is recognized by hypoperfusion of several organ systems. The initial diagnosis is suggested by altered level of consciousness, decreased urine output, mottled skin, and hemodynamic instability. Hypotension is a frequent accompaniment of shock; however, some patients will have preserved systolic pressure in the face of severe shock early on as a result of excessive catecholamine release. Sedating the patient will often unmask hypotension, a physiologic response that should be anticipated.

Classification of shock

The causes of shock can be classified as hypovolemic, vasodilatory, and cardiogenic (Table 1). Hypovolemic and vasodilatory shock are due to inadequate venous return to the heart; cardiogenic shock is due to pump failure. Inadequate venous return occurs because of lack of circulating volume that is due to hemorrhage or dehydration (hypovolemic shock), or because of widespread vasoplegia, or lack of vascular tone (vasodilatory shock). Pump failure (cardiogenic shock) can be due to loss of contractility (myocardial infarction and its complications); impaired diastolic filling; abnormal rate or rhythm; or obstruction to flow that is due to valvular conditions, pulmonary embolus, or tamponade. Vasodilatory shock has many causes, including sepsis, anaphylaxis, poisoning, and ischemia reperfusion syndrome that is due to prolonged shock of any cause.

Hypovolemic shock is recognized clinically by signs of hypoperfusion, such as altered mentation; poor urine output; and cool, mottled extremities. The jugular venous pressure is low, capillary refill is poor, and there is a narrow pulse pressure that is indicative of reduced stroke volume. Hypovolemic shock is often suggested by the clinical setting (trauma, childbirth, gastrointestinal bleeding), clinical manifestations of

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Table 1
Rapid formulation of a working diagnosis for the cause of shock

	High-output hypotension: vasodilatory shock	Low cardiac-output hypotension: cardiogenic and hypovolemic shock
Is cardiac output reduced?	No	Yes
Pulse pressure	Wide	Narrow
Diastolic pressure	Extremely low	Low
Extremities, digits	Warm	Cool
Nailbed return	Rapid	Slow
Heart sounds	Crisp	Muffled
Temperature	Abnormally high or low	Normal
White blood cell count	Abnormally high or low	Normal
Site of infection	Present	Absent
	Reduced pump function: cardiogenic shock	Reduced venous return: Hypovolemic shock
Is the heart too full?	Yes	No
Symptoms, clinical context	Angina, abnormal ECG	Blood loss, volume depletion
Jugular venous pressure	High	Low
Gallop rythm	Present	Absent
Respiratory examination	Crepitations	Normal
Chest radiograph	Large heart, pulmonary edema	Normal
What does not fit?		
Overlapping causes	High right atrial pressure hypotension	Nonresponsive hypovolemia
Septic cardiogenic	High right sided pressure, clear lungs	Adrenal insufficiency
Septic hypovolemic	Pulmonary embolus	Anaphylaxis
Cardiogenic hypovolemic	Right ventricular infarction	Neurogenic shock
	Cardiac tamponade	

Adapted from Walley KR, Wood LDH. Shock. In: Hall JB, Schmidt GA, Wood LDH, editors. Principles of critical care. 2nd edition. New York: McGraw-Hill, Health Professions Division; 1998. p. 278; with permission.

blood loss (hematemesis, tarry stools, abdominal distension), or dehydration (vomiting, diarrhea, thirst). Rapid and appropriate replacement of fluids that have been lost quickly restore organ perfusion and confirm the diagnosis.

Cardiogenic shock is recognized clinically by evidence of global hypoperfusion (altered mentation, mottled extremities, poor urine output), a narrow pulse pressure, and elevated jugular venous pressure. There also may be evidence of pulmonary edema and a gallop in the case of left heart failure. Cardiogenic shock occurs in the clinical setting of sudden collapse or chest pain, and usually is accompanied by ECG changes and radiographic abnormalities. Confirmatory tests, such as echocardiography, cardiac catheterization, or helical CT scanning (if pulmonary embolism is suspected) are urgently indicated because ultimate successful management requires specific interventions.

Vasodilatory shock can occur in a variety of settings, the most common being sepsis. Initially, patients who have vasodilatory shock have clinical findings that are similar to those in patients who have hypovolemic shock. The key difference is the lack of complete reversal with fluid administration. Often, several liters of crystalloid are infused with little effect on blood pressure, mentation, or urine output. Hyperemic extremities, bounding pulses, brisk capillary refill, hyperdynamic heart sounds, and a wide pulse pressure that is indicative of a large stroke volume mark the clinical response to fluid in vasodilatory shock.

Vasodilatory shock is also a final common pathway to multiple organ dysfunction from a variety of causes, including burns, pancreatitis, carbon monoxide and cyanide poisoning, and anaphylaxis. Prolonged shock from any cause can lead to ischemia-reperfusion injury [1–3], the hallmark being the presence of an inflammatory response.

The primary survey

The primary survey of a critically ill patient in shock should include assessing and establishing an airway, evaluating breathing and consideration of

mechanical ventilator support, and resuscitating the inadequate circulation.

Airway and breathing

Most patients in shock have one or more indications for airway intubation and mechanical ventilation, which should be instituted early on, often before a blood gas is obtained. Significant hypoxemia is one indication for intubation and mechanical ventilation, because external masks may not deliver reliably an adequate fraction of inspired oxygen (F_{IO_2}). Initially, a high F_{IO_2} should be administered until serial blood gas or pulse oximetry determinations allow a downward titration of oxygen therapy to less toxic levels. This is relevant in many patients because pulmonary injury, acute respiratory distress syndrome, can occur early in shock as a result of the development of an intense inflammatory response.

Ventilatory failure should be recognized early in a patient who is clinically failing, even before blood gases are obtained. Although a high and increasing P_{CO_2} on arterial blood gas measurement is diagnostic, it is important to recognize ventilatory failure clinically, even in the absence of an elevated P_{CO_2}. Evidence of respiratory muscle fatigue includes labored breathing, inability to speak, tachypnea or an inappropriately low and falling respiratory rate, paradoxical abdominal respiratory motion, accessory muscle use, diaphoresis, and cyanosis. Ventilatory failure also should be anticipated in patients who manifest a severe metabolic acidosis in association with shock, because they will eventually lose their ability to compensate for a variety of reasons, including respiratory muscle fatigue, mental obtundation, and sedative drugs. Accordingly, the indications for airway intubation and mechanical ventilation can be anticipated and often are clinically apparent in the absence of further diagnostic tests and procedures.

Patients in shock often fail to protect their airway. This is an important indication for intubation, particularly before procedures or transport of the patient, when the ability to rapidly intubate is suboptimal. Airway intubation and mechanical ventilation, along with sedation and paralysis, will decrease oxygen demand of the respiratory muscles and allow improved oxygen delivery to other hypoperfused tissue beds [4]. This is important during shock because respiratory muscles consume a disproportionate share of the whole body oxygen delivery, particularly in patients who are tachypneic as a result of acidosis, sepsis, pain, or hypoxemia. Thus, multiple organ hypoperfusion (the definition of shock) is an indication for intubation and mechanical ventilation to redistribute blood flow from respiratory muscles to vital organs.

Circulation: volume therapy is the cornerstone of initial management of shock

Based on the initial assessment of the patient in shock, the clinician formulates a working diagnosis. If the working diagnosis is hypovolemia, the indicated intervention is a volume challenge. The rate and composition of the volume expanders is determined by the working diagnosis. Hemorrhagic shock requires immediate hemostasis and rapid infusions of warmed blood substitutes (red cells, plasma, platelets, albumin). Hypovolemic shock that is due to dehydration requires rapid boluses of crystalloid, usually in increments of one liter. Cardiogenic shock without evidence of fluid overload requires smaller volume challenges, usually 250 mL of crystalloid. In vasodilatory shock, surprisingly large volumes of crystalloid are required, often 6 L to 10 L. Some clinicians change to colloid boluses (either albumin or pentastarch) to reduce the inevitable tissue edema that accompanies the capillary leak that is associated with this state, although evidence for the clinical benefit of this approach is controversial [5].

Regardless of the diagnosis or the fluid therapy chosen, the adequacy of volume expansion should be observed by titrating to an easily observable clinical endpoint, either benefit (increased blood pressure, decreased heart rate, increased pulse pressure, increased urine output) or harm (pulmonary edema, evidence of right heart dysfunction). Absence of either response indicates that the volume challenge was inadequate and ensuing volume challenges should continue with rapid clinical reassessment of the response.

Because ''time is tissue'', volume resuscitation should be rapid. The effects of a liter saline infusion over 10 minutes can be readily identified and interpreted and lead to further similar infusions, if necessary. In contrast, infusion of a liter of normal saline over 1 hour does not reverse hypovolemic shock at an adequate pace and, in view of the many concurrent interventions and redistribution of saline to the entire extracellular compartment, the clinical response is often difficult to assess.

Circulation: vasoactive therapy should be simplified and goal-directed

Too often, ''blanket'' vasoactive therapy is applied early in shock without regard to the clinical diagnosis or the volume status of the patient. This strategy confounds the determination of an adequate circulat-

ing volume as well as the cause of shock. Accordingly, we encourage early, rapid, aggressive volume resuscitation followed by vasoactive therapy if still required.

The choice of vasoactive therapy is surprisingly simple. The clinician must determine whether there is evidence of low cardiac output with high cardiac filling pressures that requires inotropic support or if hypotension is accompanied by a high cardiac output state that requires pressor support. Adequate cardiac output is more important than blood pressure, because adequate tissue oxygen delivery is the underlying goal. Adequate distribution of flow, however, depends on an adequate pressure head. At pressures that are less than an autoregulatory limit, normal flow distribution mechanisms are lost; significant organ system hypoperfusion may persist in the face of elevated cardiac output owing to maldistribution of flow. This is the problem in vasodilatory (or septic) shock.

Generally, β-adrenergic agonists are chosen for support of cardiac contractility and α-adrenergic agonists are chosen when maintenance of perfusion pressure is needed to maintain flow distribution to the tissues (Fig. 1). Commonly-used α-agonists are phenylephrine or norepinephrine. Norepinephrine increases mean arterial pressure at the expense of cardiac output,

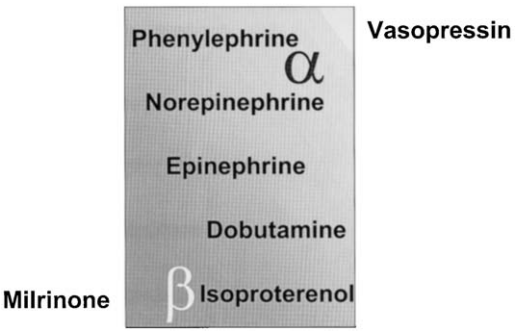

Fig. 1. Approach to vasoactive therapy. This simplified approach to vasoactive therapy emphasizes differentiation between α-adrenergic agonists that primarily have a pressor effect (pressure) and β-adrenergic agonists (β) that primarily have an inotropic effect (flow). Phenylephrine is a pure α-agonist that causes vasoconstriction. Norepinephrine is primarily α, but has some β properties as well. Epinephrine is a powerful vasoconstrictor and positive inotropic agonist and is used in severe shock and impending cardiac arrest. Dobutamine has positive inotropic and vasodilating properties and is useful to enhance cardiac output in a well volume-resuscitated patient. Isoproterenol is a pure β-agonist and is used for its positive chronotropic properties in complete heart block.

When α-receptors are down-regulated and the patient no longer responds to α-adrenergic pressor agonists, vasopressin is an alternative because it has a pressor effect by way of the V1 receptor [56].

and, therefore, is used only when cardiac output is adequate or increased. Dobutamine is a common choice of a β-adrenergic agonist. Dobutamine increases cardiac output but vasodilates the vasculature so that blood pressure will drop unless venous return is augmented. If this occurs, a volume bolus is usually needed to restore blood pressure.

When β-adrenergic receptor down-regulation occurs and dobutamine is no longer effective, an alternative choice is a phosphodiesterase inhibitor, such as milrinone or amrinone. These agonists bypass the β-adrenergic receptor and act to directly increase cyclic AMP levels and increase cardiac contractility.

α-adrenergic agents are the treatment of choice for vasodilatory states when restoration of perfusion pressure is the goal. The primary α-adrenergic agents are phenylephrine and norepinephrine (see Fig. 1). Epinephrine may be used in severe shock and during acute resuscitation because it has α- and β-adrenergic effects. Prolonged use leads to flow inequalities and tissue ischemia [6,7]; therefore, most clinicians step down therapy quickly. In 50 years of using pressors for vasodilatory shock, there has not been a randomized controlled trial of any pressor agent versus any other [8].

We recommend choosing a vasoactive agent with which the clinician is familiar (Table 2). The dose should be titrated to either systolic or mean arterial pressure that achieves the goal of restoring autoregulation as assessed clinically by evidence of adequate organ perfusion. Concurrently, it is essential to confirm adequacy of cardiac output by measuring cardiac output, central venous oxygen saturation, and other indicators, such as lactate and acid base status.

Time is tissue: the evidence

There is ample evidence to support the intuitive hypothesis that timely reversal of the shock state will prevent development of multiple organ failure and death. The ‘‘time is tissue’’ hypothesis has been borne out by the many trials of thrombolysis in myocardial infarction [9], in treatment of massive pulmonary embolism [10], and in a randomized clinical trial of goal-directed therapy for septic shock [11].

Recently, Kern and Shoemaker [12] reviewed 21 randomized controlled studies that described hemodynamic goals in acute, critically ill patients to evaluate the various influences that contributed to outcome. They identified seven studies in which the mortality in the control group was at least 20% and therapy was used before the onset of organ failure. In these studies, goal-directed therapy that was based on invasive

Table 2
Vasoactive therapy in shock states

Agent	Hemodynamic response	Usual dosage range
Dopamine	↑ Cardiac contractility	5–10 υg/kg/min
	↑ Systemic pressure, ↑ heart rate	10–25 υg/kg/min
Phenylephrine	↑ Systemic pressure	40–180 υg/kg/min
Norepinephrine	↑ Systemic pressure	1–30 υg/kg/min
Epinephrine	↑ Systemic pressure	1–10 υg/kg/min
	↑ Cardiac contractility	
Dobutamine	↑ Cardiac contractility	2.5–10 υg/kg/min
	↓ Systemic pressure	
Milrinone	↑ Cardiac contractility	0.25–1.0 υg/kg/min
	↓ Systemic pressure	
Vasopressin	↑ Systemic pressure	0.01–0.04 U/min

1 υg/dL = 27.59 nmol/L.

hemodynamic monitoring to achieve supranormal goals was associated with a 23% absolute risk reduction in mortality ($P < 0.05$). There was no difference in mortality associated with goal-directed hemodynamic monitoring in less sick patients or in patients in whom organ failure had already occurred. They concluded, based on the studies, that increased cardiac index (CI) and oxygen delivery with a pulmonary arterial occlusion pressure of less than 18 mm Hg should be goals of therapy. When implemented early and aggressively, goal-directed therapy reduces mortality in critically ill patients. Goal-directed therapy to achieve optimal goals is ineffective in the late stages after onset of organ failure because no amount of extra oxygen will restore irreversible oxygen debt or reverse cellular death.

Rivers and colleagues [11] conducted a randomized, controlled trial of 263 patients who had severe sepsis or septic shock to study the application of early goal-directed therapy using a central venous catheter. Patients who were randomized to early goal-directed therapy were managed for the first 6 hours in the emergency department. All patients were intubated, ventilated, and sedated as necessary. In the group that received early goal-directed therapy, crystalloid or colloid was infused to achieve a central venous pressure (CVP) of 8 mm Hg to 12 mm Hg and vasoactive agents were infused to achieve a mean arterial pressure of at least 65 mm Hg. Central venous oxygen saturation ($S_{CV}O_2$) was measured through the central venous catheter and was used as a surrogate of cardiac output. A low $S_{CV}O_2$ correlates with low cardiac output and a high $S_{CV}O_2$ correlates with high cardiac output [13]. If the $S_{CV}O_2$ was less than 70%, red cells were transfused until the hematocrit was greater than 30%. If the $S_{CV}O_2$ remained low, inotropic agonists (dobutamine) were infused to achieve an $S_{CV}O_2$ of at least 70%. During the initial 6 hours of therapy, the patients who were assigned to early goal-directed therapy received significantly more fluid than those who were assigned to standard therapy ($P < 0.001$), more red-cell transfusions ($P < 0.001$), and more inotropic support ($P < 0.001$), whereas similar proportions in the two groups received vasopressors and mechanical ventilation. Hospital mortality was significantly lower in the group that received early goal-directed therapy compared with the group that received standard therapy (30.5% versus 46.5%, $P = 0.009$) as was 28-day mortality (33.3% versus 49.2%, $P = 0.01$) and 60-day mortality (44.3% versus 56.9%, $P = 0.03$). The proposed reason for these advantages was a significantly higher mean central venous saturation (77% versus 66%). This was achieved through increased use of fluids (5 L versus 3.5 L), blood (64% versus 19%), and dobutamine (14% versus 1%) during the first 6 hours of care in the emergency department. Thus, early aggressive resuscitation improves outcome in septic shock.

The meta-analysis by Kern and Shoemaker demonstrated that goal-directed hemodynamic monitoring, using a pulmonary artery catheter to achieve supranormal oxygen delivery, is effective in critically ill patients if used before the onset of organ failure. The study by Rivers and colleagues highlights two important principles; resuscitation must be initiated early and be goal-directed to be effective. We do not favor one approach (use of a pulmonary artery catheter and measurement of cardiac index and oxygen delivery) over the other (use of a central venous catheter and measurement of $S_{CV}O_2$ to guide therapy). The application of hemodynamic monitoring will depend on user familiarity, skill level, and resources. The goals of therapy should be individualized. The most important aspect of using hemodynamic monitoring to optimize therapy is to have goals that are clearly defined

Table 3
Causes of shock

Low cardiac output hypotension		High cardiac output hypotension	
Cardiogenic shock	Hypovolemic shock	Vasodilatory shock	Unique causes of shock
Left ventricular failure	Reduced mean systemic pressure	Septic shock	Adrenal insufficiency
Systolic dysfunction	Intravascular hypovolemia	Hepatic failure	Hemoglobin and mitochondrial poisons
Myocardial infarction	Hemorrhage	Arteriovenous shunts	Cyanide
Ischemia and global hypoxemia	Gastrointestinal	Dialysis	Carbon monoxide
Cardiomyopathy	Trauma	Paget's disease	Iron intoxication
Depressant drugs	Aortic dissection	Thyroid storm	Phaeochromocytoma
Beta-blocker overdose	Other internal sources	Ischemia-reperfusion injury (Prolonged shock of any cause)	
Calcium channel blockers	Renal Losses	Postcardiopulmonary bypass	
Myocardial contusion	Diuresis osmotic, drug-induced diabetes: insipidus, mellitus		
Respiratory acidosis	Gastrointestinal losses		
Metabolic derangements: acidosis, hypophosphatemia, hypocalcemia	Vomitting		
Diastolic dysfunction	Diarrhea		
Ischemia and global hypoxemia	Gastric suctioning		
Ventricular hypertrophy	Surgical stomas		
Restrictive cardiomyopathy	Extravascular redistribution		
Ventricular interdependence	Burns		
Greatly increased afterload	Sepsis		
Aortic stenosis	Trauma		
Hypertrophic cardiomyopathy	Postoperative		
Dynamic outflow obstruction	Decreased venous tone		

- Coarctation of the aorta
- Malignant hypertension
- Valve and structural abnormality
- Mitral stenosis
- Endocarditis
- Severe mitral/aortic regurgitation
- Atrial myxoma/thrombus
- Papillary muscle rupture
- Ruptured septum of free wall

Right ventricular failure
- Decreased contractility
- Right ventricular infarction
- Ischemia and global hypoxemia
- Greatly increased afterload
- Pulmonary embolism
- Pulmonary vascular disease
- Hypoxic Pulmonary Vasoconstriction
- Mechanical ventilation/ high PEEP
- Valvular and structural disease
- Obstruction: atrial myxoma, thrombus

Arrhythmias

Drugs
- Sedatives
- Narcotics
- Anaphylactic shock
- Neurogenic shock

Increased resistance to venous return
- Cardiac tamponade
- Pericardial fluid collection
- Blood
- Renal failure
- Pericarditis with effusion
- Constrictive pericarditis
- High intrathoracic pressure
- Tension pneumothorax
- Massive pleural effusion
- Mechanical ventilation/PEEP
- High intra-abdominal pressure
- Ascites
- Massive obesity
- Abdominal trauma/surgery

Abbreviation: PEEP, positive end-expiratory pressure.

Adapted from Walley KR, Wood LDH. Shock. In: Hall JB, Schmidt GA, Wood LDH, editors. Principles of critical care. 2nd edition. New York: McGraw-Hill, Health Professions Division; 1998. p. 286; with permission.

whether they are physiologic (eg, urine output, skin perfusion) or measured (eg, CVP, oxygen saturation, CI). Also, hemodynamic monitoring should be promptly discontinued when the information obtained no longer guides therapy.

The secondary survey: a search for the definitive cause of shock

Completion of the primary survey, formulation of a working hypothesis, and institution of initial resuscitative efforts allow the clinician a pause to consider the definitive cause of shock. The outcome of initial tests and response to early resuscitative efforts dictates the next therapeutic intervention or invites a refined or alternative explanation for the hypoperfused state of the patient. Accurate formulation of a clinical hypothesis (see Table 1) leads to more rapid and efficient patient care.

Several classifications of shock are possible. We emphasize inadequate organ system perfusion and hypotension (Table 3). Inadequate perfusion can result primarily from decreased pump function of the heart, decreased venous return despite normal pump function, or high cardiac output hypotension that is caused by reduced vascular tone that is associated with abnormal blood flow distribution.

Shock that is caused by decreased pump function of the heart is termed ''cardiogenic shock'' and commonly results from left ventricular ischemia; however, acute valvular dysfunction should always be considered and urgent echocardiography is indicated. Common contributors to cardiac dysfunction include hypoxia and metabolic derangements, which should be quickly excluded or corrected. Finally, poisoning with cardiodepressant drugs can cause profound cardiac failure and have specific therapeutic options.

Cardiogenic shock can also result from acute right heart failure and should be suspected in the setting of high right-sided pressures and the absence of pulmonary edema. Massive pulmonary embolism is a common cause as is right ventricular infarction. Echocardiography confirms the diagnosis. Arrhythmias can cause cardiogenic shock; however, a common mistake is to treat tachyarrhythmias in the setting of shock, only to further decrease cardiac output. Cardiac output is the product of stroke volume and heart rate. When stroke volume is fixed (eg, in acute right heart failure), cardiac output is rate-dependent. Therefore, we caution against slowing the heart unless it is clear that the tachyarrhythmias or myocardial ischemia is the cause of shock and other conditions reducing stroke volume have been excluded.

Hypovolemic shock from intravascular hypovolemia is usually suggested by the clinical presentation. Aortic dissection and other sources of internal bleeding, such as ruptured ectopic pregnancy, should always be in the differential diagnosis of unexplained hypovolemic shock; these sources should be investigated by the imaging modality that is rapidly available. Hypovolemic shock from decreased venous tone can be due to drugs and requires a high index of suspicion. Cardiac tamponade can either be classified as a cardiogenic shock or as increased resistance to venous return; it presents as high right-sided pressures, muffled heart sounds, and occurs in the setting of malignancy, renal failure, and trauma. Echocardiography is the modality of choice for investigation. Other causes of increased resistance to venous return include intrathoracic emergencies, such as tension pneumothorax and high end-expiratory pressures, that occur in status asthmaticus and mechanical ventilation. Increased abdominal pressure, known as ''abdominal compartment syndrome,'' is suggested by the triad of high ventilatory pressures, a tense abdomen, and oliguria [14]. It occurs commonly in trauma and abdominal surgery and is associated with massive fluid resuscitation, such as ruptured abdominal aortic aneurysm. The clinical suspicion can be confirmed by transducing the bladder pressure; urgent surgical decompression is indicated if the intra-abdominal pressure exceeds 35 cm H_2O.

Vasodilatory shock is commonly due to sepsis, which should always be rapidly investigated; empiric therapy should be started based on the clinical suspicion of the source of sepsis. Prolonged shock from any cause has an inflammatory component and is termed ''ischemia-reperfusion'' injury [1–3]. Other causes are listed (see Table 3); the clinical setting usually aids in the diagnosis.

Finally, if the clinical presentation does not fit with any of the aforementioned causes, unique causes of shock should be considered. Several acute endocrinologic conditions can present as shock. Acute adrenal insufficiency can present as shock in many settings including trauma, hemorrhage [15], childbirth (Sheehan's syndrome) [16], and adrenal insufficiency of sepsis [17]. Severe thyroid storm may lead to irreversible cardiovascular collapse, especially in the older patient who may have atypical features of thyrotoxicosis [18]. Pheochromocytoma is an explosive clinical syndrome that is characterized by severe hypertension associated with cardiac complications, hypotension, or even shock and sudden death. The key to diagnosing pheochromocytoma is to suspect it, then confirm it [19]. Other unusual causes of shock, including cyanide, carbon monoxide, and iron poisoning, are

suggested by the clinical setting and require specific therapy.

More commonly, the patient present with more than one cause for shock (eg, cardiogenic shock complicated by sepsis that is due to aspiration pneumonia, septic shock complicated by myocardial dysfunction, and septic shock that is associated with volume depletion) (see Table 1). Our case presentation illustrates this concept.

Case presentation

A 59 year-old male was found after an unwitnessed collapse at home. Paramedics reported an obtunded male with a weak, thready pulse and unobtainable blood pressure. He was breath rate was 6/minute. Emergency resuscitation consisted of administration of oxygen by high-flow mask and administration of 1 L of crystalloid by peripheral vein. He was transported to a hospital emergency room where initial examination revealed a well-nourished white male with cool, mottled extremities; sluggish capillary refill; and muffled heart sounds. The blood pressure was 80/60. Neurologically, he was obtunded but moving all four limbs spontaneously. An urgently obtained ECG showed S-T segment elevation in the anterior leads, which was changed from previous ECG. His resuscitation included intubation, mechanical ventilation, and further crystalloid administration. A catheter was placed in the right internal jugular vein with an initial pressure reading of 20 mm Hg. A Foley catheter and nasogastric tube was inserted. Chest radiograph confirmed correct endotracheal, central venous, and nasogastric catheter placement, as well as an enlarged heart and evidence of pulmonary edema. Urgent echocardiography was obtained and showed a hypokinetic anterior left ventricular wall.

The provisional diagnosis was acute anterior myocardial infarction with cardiogenic shock. The patient was administered aspirin by nasogastric tube and transported to the cardiac catheterization lab for urgent angiography. Successful revascularization of an occluded left anterior descending coronary artery was performed. A right heart catheter was placed during the procedure. After the procedure, the patient was transported to the cardiac intensive care unit (ICU) in stable condition.

Over the next 6 hours, the patient became increasingly hypotensive with poor urine output. Physical examination revealed warm, but mottled, extremities; brisk capillary refill; bounding pulses; and a wide pulse pressure (80/30 mm Hg) with a low mean arterial pressure (45 mm Hg). Invasive hemodynamic measurements indicated a normal CVP, an elevated cardiac output, and low systemic vascular resistance, which were consistent with the clinical impression of vasodilatory shock. Cultures of blood, urine, and sputum were obtained and broad-spectrum antibiotics were administered. Norepinephrine was administered to keep the mean arterial pressure between 60 mm Hg and 65 mm Hg.

Over the next 2 days, renal and neurologic function improved, vasoactive medication was weaned, and the patient was liberated from mechanical ventilation. The right heart catheter was removed when fluid administration no longer depended on interpretation of the measurements. Cultures were negative after 48 hours and antibiotics were discontinued. The patient was transferred to the cardiac ward for routine postmyocardial infarction management.

Case discussion

This case demonstrates at least two types of shock present in one patient. Initially, the clinical impression was that of cardiogenic shock. Therapy consisted of application of the ABCs of resuscitation, careful fluid administration, and urgent consideration of revascularization, which was successful. Postrevascularization, the patient developed vasodilatory shock. An important cause of vasodilatory shock is sepsis, which was rapidly investigated and empirically treated. Other causes include anaphylaxis and adrenal insufficiency, which did not fit with this clinical presentation. Ischemia reperfusion injury can cause vasodilatory shock and presents as an inflammatory state after prolonged shock of any cause; that was the likely cause in this scenario. The treatment consists of supportive care and administration of pressor agents to maintain perfusion pressure to vital organs.

This case highlights the importance of clinical examination in decision-making. Invasive monitoring often confirms the clinical hypothesis and improves the clinician's confidence in the diagnosis. Invasive monitoring and support were withdrawn as soon as possible to prevent complications of the patient's intensive care stay.

Definitive management of shock

Definitive management of shock is preceded by establishing a working hypothesis and rapid stabilization of the patient with initial resuscitative efforts. We now discuss the specifics of management of three common causes of shock — hemorrhagic shock,

cardiogenic shock, and septic shock — and discuss the use of sodium bicarbonate in the treatment of shock of any cause.

Hemorrhagic shock

The goals of therapy in hemorrhagic shock are to restore oxygen perfusion to the tissues and stop hemorrhage, usually through operative intervention. Although rapid transport of the patient to definitive care is universally agreed on, controversy exists as to the timing and delivery of fluid therapy in traumatic hemorrhage [20,21].

The classic approach to hemorrhagic shock that is due to trauma has focused on early, aggressive resuscitation with large volumes of crystalloid and blood products [22]. The rationale for this is based on data from experimental work on an animal model known as the ''Wigger's preparation,'' in which animals were bled from an intravascular catheter for prolonged periods of time before resuscitation [23]. Two important observations were made; first, to induce ''irreversible shock'', animals had to be subjected to several hours of hypotension, which included a period of severe hypotension (45 minutes of mean arterial pressure of 30–40 mm Hg). Second, prolonged hemorrhagic hypotension induced an extracellular fluid volume deficit that could be corrected by administration of crystalloid in volumes of two to three times the estimated blood loss; this resulted in improved survival [24]. This is the basis for the well-known ''3:1 rule'' in the crystalloid resuscitation of hemorrhagic shock. In the last decade, this experimental model and approach to hemorrhagic shock has been questioned.

In the current animal model of hemorrhagic shock, the ''uncontrolled'' or ''vascular'' model, animals are bled through a fixed vascular lesions or a solid organ injury. Hemorrhage volume and duration depend on the animal's physiologic response (ie, thrombus formation and vasoconstriction, rather than closure of a stopcock) [21]. The first investigators to evaluate the effects of conventional rapid volume expansion bled swine from a 5 cm tear in the infrarenal aorta [25]. The treatment group received lactated Ringer's solution in a volume equal to three times the estimated blood loss; the 2-hour mortality rate was 100%. Control animals were not resuscitated and experienced lower hemorrhage volumes and a 0% 2-hour mortality rate. These data suggest that one can make a nonlethal injury lethal by overresuscitating before active bleeding has been stopped.

Observational studies from the literature suggest that aggressive resuscitation with fluid before definitive surgical management may not be beneficial; in fact, it may be detrimental in humans. The first large series reported was on the effect of prehospital intravenous fluids on survival in 6855 patients who had experienced trauma [26]. The volume of fluid administered was not significantly different in the group who survived compared with those who died, when matched for severity of illness. Although hypotension was associated with a significantly higher mortality rate, the administration of fluids had no influence on this rate. In 1994, Bickell and coworkers [27] reported results of a prospective trial that compared immediate and delayed fluid resuscitation in 598 adults who had penetrating torso injuries who presented with a prehospital systolic blood pressure of at least 90 mm Hg. The group whose fluid resuscitation was delayed had better survival (70% versus 62%, $P = 0.04$), fewer complications, and shorter hospital stays. The findings were attributed to accentuation of ongoing hemorrhage or hydraulic disruption of an effective thrombus, followed by a fatal secondary hemorrhage. The recommendation was to delay aggressive fluid resuscitation in hypotensive patients who had penetrating torso injury until the time of operative intervention. Several problems with this study were noted, including the lack of randomization [28] and differences in mean arterial pressure between the two groups just before surgery [29]. Nonetheless, the results of this study raised questions about the value of aggressive fluid resuscitation in injured patients who have hypotension of presumed hemorrhagic origin.

Studies that have occurred since Bickell et al's contribution, however, support the conclusion that moderate resuscitation is best for uncontrolled vascular injury, whether the end point is cardiac index and oxygen delivery, the observation period is longer, the fluid chosen is crystalloid or blood, the replacement ratio of crystalloid:blood loss is altered, crystalloids and hypertonic/colloid solutions are used, or traumatic brain injury is present [20]. In an animal study of uncontrolled venous hemorrhage, moderate, instead of no, resuscitation was associated with improved regional blood flow [29]. The investigators reported that increasing the volume of fluid resuscitation did not improve tissue perfusion in the heart, liver, kidney, or intestines. In fact, resuscitation with larger volumes of crystalloid after uncontrolled venous hemorrhage resulted in significantly decreased liver perfusion compared with the animals that had limited volume resuscitation. This area remains controversial and was suggested that ''the evidence is insufficient to refute the many observations that adequate volume resuscitation is an effective mode of therapy as long as it does not delay surgical intervention'' [28]. Several questions remain, not the least of which is, ''What is the

long-term effect of limited hypotensive resuscitation?'' Are we trading improved short-term survival for the development of multiple system organ failure and poor neurologic outcome?

Cardiogenic shock

Cardiogenic shock is a state of inadequate tissue perfusion that is due to cardiac dysfunction, often myocardial infarction. The mortality from cardiogenic shock is high, between 50% and 80% [30], and may be underestimated because many patients die before transport to the hospital. The mortality from cardiogenic shock may be decreasing because of the recent trend toward aggressive revascularization strategies [31].

The initial approach to the patient who is in cardiogenic shock should include fluid resuscitation, unless pulmonary edema is present [32]. After the primary survey and initial resuscitative measure have been instituted and vasoactive therapy considered, urgent echocardiography aids in excluding tamponade and acute valvular dysfunction.

Cardiogenic shock that complicates myocardial infarction dictates urgent consideration of revascularization. Unfortunately, no trials have demonstrated that thrombolytic therapy reduces mortality in patients who have confirmed cardiogenic shock, although it makes intuitive sense. The numbers of patients in these trials were too small to draw any conclusions because most thrombolytic trials excluded patients who had cardiogenic shock at presentation [33].

Early revascularization for cardiogenic shock was evaluated in a randomized trial in which 152 patients were assigned to revascularization (angioplasty in 64%, cardiac surgery in 36%) and 150 patients were assigned to medical treatment (including thrombolysis and intra-aortic balloon counterpulsation) [34]. Six-month mortality was lower in the group that had revascularization (50.3% versus 63.1%, $P = 0.027$). This survival advantage was still significant at 1 year [35]. Of the 10 prespecified subgroup analyses, only age (younger than 75 versus 75 years or older) interacted significantly ($P < 0.03$) with treatment; treatment benefit was apparent only for patients who were younger than 75 years (51.6% survival in the group that had early revascularization group versus 33.3% in group that received medical therapy) [35]. The investigators recommended rapid transfer of patients who had acute myocardial infarction that was complicated by cardiogenic shock, particularly those who were younger than 75 years, to medical centers that are capable of providing early angiography and revascularization procedures. In hospitals without direct angioplasty capability, stabilization with intra-aortic balloon pump counterpulsation and thrombolysis, followed by transfer to a tertiary care facility may be the best option [32].

Septic shock

Septic shock is defined as sepsis-induced hypotension despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or acute alteration in mental status [36,37]. Initial management consists of fluid therapy, and, often, institution of vasopressor therapy. Definitive therapy includes empiric antibiotic therapy after appropriate cultures have been obtained and surgical management of necrotic tissue and loculated infectious processes. Despite this approach, the mortality rate that is associated with septic shock has changed little over time [38].

Corticosteroids in septic shock

High doses of corticosteroids that are administered to septic patients do not improve survival and may worsen outcomes by increasing the frequency of secondary infections [39]. In contrast, low-dose (''physiologic'') steroids in patients who have septic shock may be beneficial because of relative adrenal insufficiency [40–42].

High-dose steroid therapy in septic shock was associated with higher numbers of infectious complications. The immunologic and hemodynamic effects of low-dose hydrocortisone in septic shock were recently investigated [42]. Hydrocortisone infusion induced an increase in mean arterial pressure and systemic vascular resistance, and a decrease in heart rate, CI, and norepinephrine requirement. A reduction of plasma nitrite/nitrate indicated inhibition of nitric oxide formation and correlated with a reduction of vasopressor support. The inflammatory response (interleukins [IL]-6 and -8), endothelial (soluble E-selectin) and neutrophil activation (expression of CD 11b, CD64), and the anti-inflammatory response (soluble tumor necrosis factor receptors I and II and IL-10) were attenuated. In vitro phagocytosis and the monocyte-activation cytokine, IL-12, increased. Hydrocortisone withdrawal induced hemodynamic and immunologic rebound effects. The investigators concluded that low-dose hydrocortisone therapy restored hemodynamic stability and differentially modulated the immunologic response to stress by way of anti-inflammation rather than immunosuppression [42].

The diagnosis of adrenal insufficiency in critically ill humans varies with the diagnostic test and the threshold value of the cortisol response to the

test. Traditionally, a cortisol response of greater than 18 υg/dL (plasma cortisol units: 1 υg/dL equals 27.59 nmol/L) to a high-dose (250 υg) corticotropin test has been regarded as a normal response to stress [43]. Marik and Zaloga [41] questioned this approach in critically ill humans who had septic shock. They demonstrated that the low-dose (1 υg) corticotropin test was more sensitive in predicting hemodynamic response (pressor discontinuation within 24 hours) than the high-dose test. Receiver operating characteristic curve analysis revealed that a stress cortisol concentration of 23.7 υg/dL was the most accurate diagnostic threshold for determination of the hemodynamic response to steroids; 61% of patients who had septic shock patients met the criteria for adrenal insufficiency when a baseline cortisol of 25 υg/dL was the diagnostic threshold. The sensitivity of a baseline cortisol that was less than 25 υg/dL in predicting steroid responsiveness was 96%, compared with 54% for the low-dose test and 22% for the high-dose test.

A randomized, controlled trial with clinical outcomes that supported low-dose steroid therapy was recently reported. Annane and coworkers [44] showed that 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients who had septic shock and relative adrenal insufficiency without increasing adverse events. In a subgroup analysis, this benefit was seen only in the group of patients who had a blunted cortisol response to high-dose adrenocorticotropin, defined as a serum cortisol increase of less than 9 υg/dL.

In summary, clinicians should not use high-dose corticosteroids in patients who have sepsis. Low-dose hydrocortisone therapy was effective in one study of patients who had septic shock but has not been confirmed by other studies. We currently recommend administration of hydrocortisone to patients who have severe septic shock that is refractory to catecholamine therapy, in conjunction with a corticotropin stimulation test. A reasonable approach is to give dexamethasone, 4 mg intravenously (IV) every 6 hours (does not interfere with cortisol assay), until a low-dose corticotropin stimulation test can be performed. A baseline cortisol level of less than 25 υg/dL in a highly stressed patient is a useful diagnostic threshold for the diagnosis of adrenal insufficiency. If the cortisol response to administration of corticotropin is blunted, regardless of the baseline cortisol, steroids should be continued.

Recombinant human activated protein C

Recombinant human activated protein C (drotrecogin alfa) is the first anti-inflammatory agent that proved effective in the treatment of sepsis [45]. Activated protein C, a component of the natural anticoagulant system, is a potent antithrombotic serine protease with substantial anti-inflammatory properties. In a recent randomized, double-blind, placebo-controlled, multicenter trial, patients who had systemic inflammation and organ failure that was due to acute infection were enrolled and assigned to receive an IV infusion of placebo or drotrecogin alfa (activated protein C) for a total of 96 hours [46]. Treatment with activated protein C was associated with a reduction in the relative risk of death of 19.4% (95% confidence interval, 6.6%–0.5) and an absolute reduction in the risk of death of 6.1% ($P = 0.005$). The incidence of serious bleeding was higher in the group that received activated protein C than in the group that received placebo (3.5% versus 2.0%, $P = 0.06$). Treatment with activated protein C significantly reduced mortality in patients who had severe sepsis (number needed to treat = 16) but may be associated with an increased risk of bleeding.

Because of the high cost of drotrecogin alfa and the concerns with bleeding, patient selection is important [47] and guidelines have been developed to enable the clinician to make decisions regarding the use of activated protein C [48]. A post-hoc analysis of the four stratified Acute Physiology and Chronic Health Evaluation II (APACHE II) quartiles revealed enhanced drug performance in the higher two (APACHE II score of at least 25, with 13% absolute reduction in mortality versus placebo) and no evidence of overall activity in the lowest of the four APACHE II quartiles. A recent cost-benefit analysis suggested that the higher two APACHE II quartiles are the optimum target for therapy [49]. The Food and Drug Administration's labeling for drotrecogin alfa (activated) recommends that it be given to patients who have severe sepsis and with a high risk of death, such as with an APACHE II score of at least 25.

Based on the results of this trial, we recommend administration of activated protein C to patients who meet all of the inclusion criteria, including evidence of end-organ dysfunction with shock, acidosis, oliguria, or hypoxemia. The drug should be given within 24 hours of the first organ failure (as done in the trial) and important exclusion criteria exist to minimize the risk of bleeding. The drug should not be given to patients who have clinical signs of mild-to-moderate sepsis who do not have evidence of end-organ injury, unless a future trial shows a clear benefit in these patients.

Vasopressin in vasodilatory shock

Vasopressin has several mechanisms of action in refractory vasodilatory shock. Vasopressin acts directly on vascular smooth muscle receptors to cause

vasoconstriction which potentiates α-agonists and blocks ATP-sensitive potassium channels (K_{ATP} channels) to restore vascular tone [50]. The only blinded, systematic evaluation of vasopressin in sepsis was recently reported by Patel and coworkers [51]. In a controlled study they compared the effects of vasopressin with norepinephrine in 24 patients who had septic shock who required vasopressor infusions. Patients who received vasopressin had a significant (80%) reduction in vasopressor requirement. The arm who received vasopressin experienced a doubling in urine output and a 75% increase in creatinine clearance. Based on current information, it seems that the replacement of vasopressin at a fixed dose can eliminate the need for catecholamine pressors in many patients. Because the clinical studies to date were small, focused on physiologic outcomes, and data on adverse effects is limited [52], we do not recommend vasopressin as first-line therapy of vasodilatory shock until completion of an adequately powered randomized, clinical trial.

Sodium bicarbonate for lactic acidosis

Lactic acidosis accompanies shock of any cause and is associated with a high mortality rate. Treatment involves discerning and correcting its underlying cause, ensuring adequate oxygen delivery to tissues, reducing oxygen demand through sedation and mechanical ventilation, and (most controversially) attempting to alkalinize the blood with IV sodium bicarbonate. Sodium bicarbonate increases the arterial pH in critically ill patients who have lactic acidosis; the impact on intracellular pH is unknown. Animal studies suggest that intracellular pH is actually lowered [53].

Concerns regarding myocardial contractility with lactic acidosis are often cited as reasons for administration of sodium bicarbonate. There have been two studies of the hemodynamic impact of sodium bicarbonate in human lactic acidosis [54,55]. Although sodium bicarbonate increased pH and serum bicarbonate concentrations, it did not improve hemodynamics or catecholamine responsiveness. Specifically, the effects of bicarbonate were indistinguishable from saline with regard to heart rate, CVP, pulmonary artery pressure, mixed venous oxyhemoglobin saturation, systemic oxygen delivery, oxygen consumption, arterial blood pressure, pulmonary artery occlusion (wedge) pressure, and cardiac output. These negative findings persisted even in the subset of patients who had the most severe acidosis (arterial pH 6.9–7.2). Given the lack of evidence supporting the use of sodium bicarbonate, we do not recommend its use for the treatment of lactic acidosis that accompanies shock of any cause, even in the face of severe acidosis ($pH < 7.2$).

Summary

Shock is an emergency that requires continuous bedside evaluation, resuscitation, and re-evaluation. The initial bedside examination allows the clinician to determine whether the patient exhibits a clinical picture that is consistent with hypovolemic, cardiogenic, or vasodilatory shock. The primary survey dictates urgent initial resuscitation that usually consists of intubation, ventilation, and volume support. Vasoactive therapy is started when the patient is well volume-resuscitated and consists of inotropic support for cardiogenic shock and pressor therapy for vasodilatory shock. The secondary survey is helpful in revealing the cause of shock and necessary to institute early definitive therapy. Early shock has a hemodynamic component, which is often easily reversed. Septic shock and prolonged shock from any cause has an inflammatory component, which is not easily reversed and leads to multiple-system organ failure (MSOF) and death. Success in treatment of shock depends on early recognition of shock and the rapid tempo of resuscitation of its hemodynamic component to prevent or minimize the inflammatory component.

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